EXHIBIT 28

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF PENNSYLVANIA

IN RE: ZOLOFT (SERTRALINE HYDROCHLORIDE) PRODUCTS LIABILITY LITIGATION	§	**MDL NO. 2342**
	§	**12-MD-2342**
THIS DOCUMENT RELATES TO ALL ACTIONS	§	**HON. CYNTHIA M. RUFE**

DECLARATION OF CYNTHIA DE LUISE

1. I am currently employed at Pfizer Inc. as a Director of Epidemiology. My immediate supervisor is Robert Reynolds, who is Vice President & Global Head of Epidemiology at Pfizer.

2. I am the author of an October 6, 2010 email, including earlier emails in an email string that began on June 11, 2010, a copy of which is attached hereto as Exhibit A.

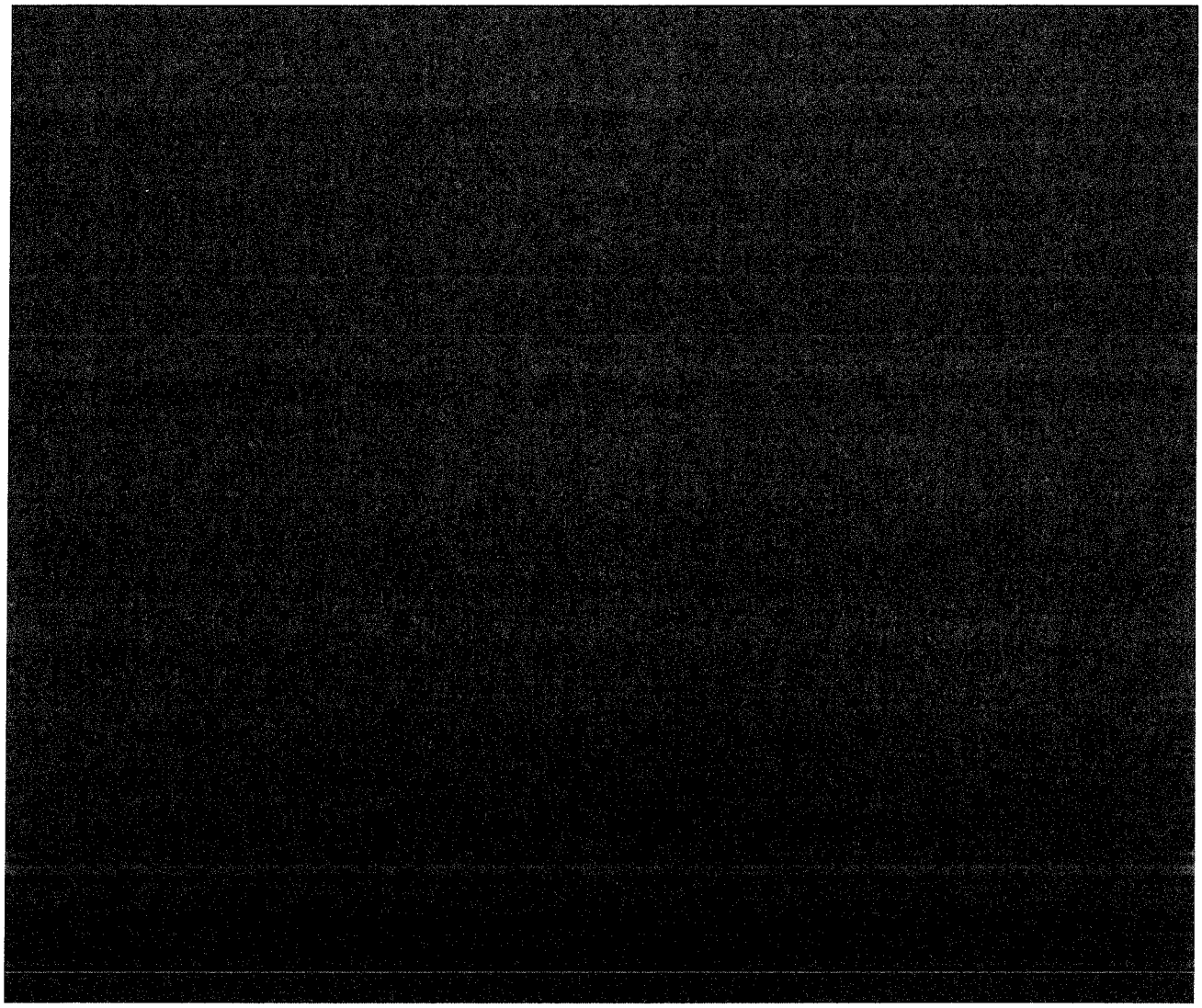
3. The emails relate to a series of events that began following a March 11, 2010, meeting of the Medicines Adverse Reactions Committee of Medsafe, the New Zealand regulatory authority for medicines and medical devices. Medsafe is New Zealand's regulatory counterpart to the Food and Drug Administration in the United States. In connection with assessing "the issue of in utero exposure to serotonin reuptake inhibitors (SSRIs and SNRIs) and risk of congenital abnormalities," in section 3.1 of the meeting minutes, attached hereto as Exhibit B, the Medsafe Committee made the following recommendations:

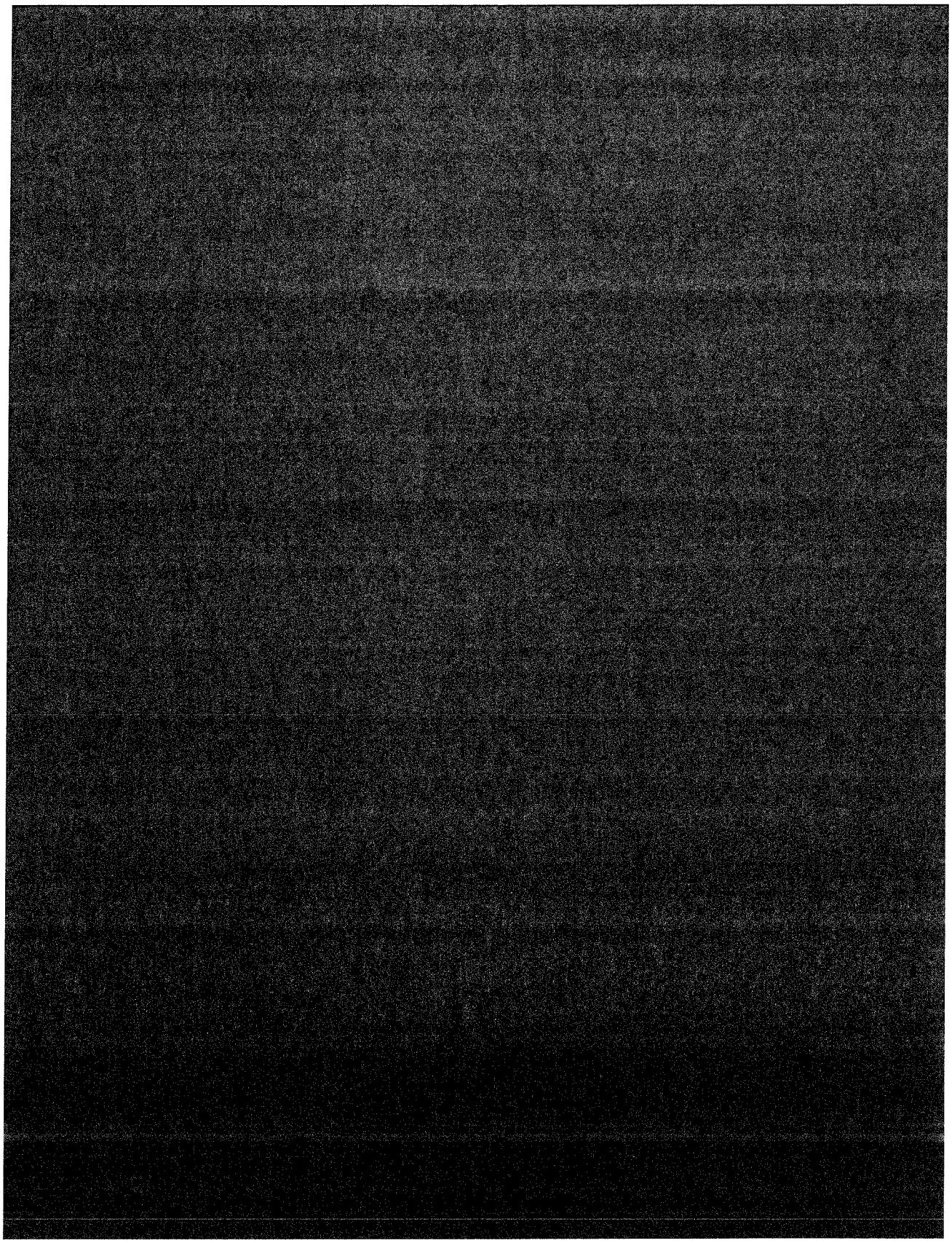
> The Committee recommended that sponsors for fluoxetine medicines be requested to update their data sheets regarding the risk of congenital anomalies when used in pregnancy. The Committee recommended that sponsors for relevant medicines other than fluoxetine and paroxetine be requested to add a general warning to the data sheets stating that there may be an increased risk of congenital abnormalities associated with SSRI (SNRI) treatment in pregnancy. The Committee recommended that a *Prescriber Update* article be written on this issue.

4. On May 24, 2010, Pfizer received a letter from Medsafe, attached hereto as Exhibit C, requesting that Pfizer include the following language in the New Zealand sertraline labeling:

> Epidemiological studies have suggested an increased risk of congenital abnormalities associated with use of SSRIs and SNRIs in pregnancy. The relevance for sertraline treatment remains unknown.
>
> Epidemiological data suggests that the use of SSRIs and SNRIs in pregnancy may be associated with a small but statistically significant increase in pre-term delivery.

This language did not originate from Pfizer, but was proposed by Medsafe.



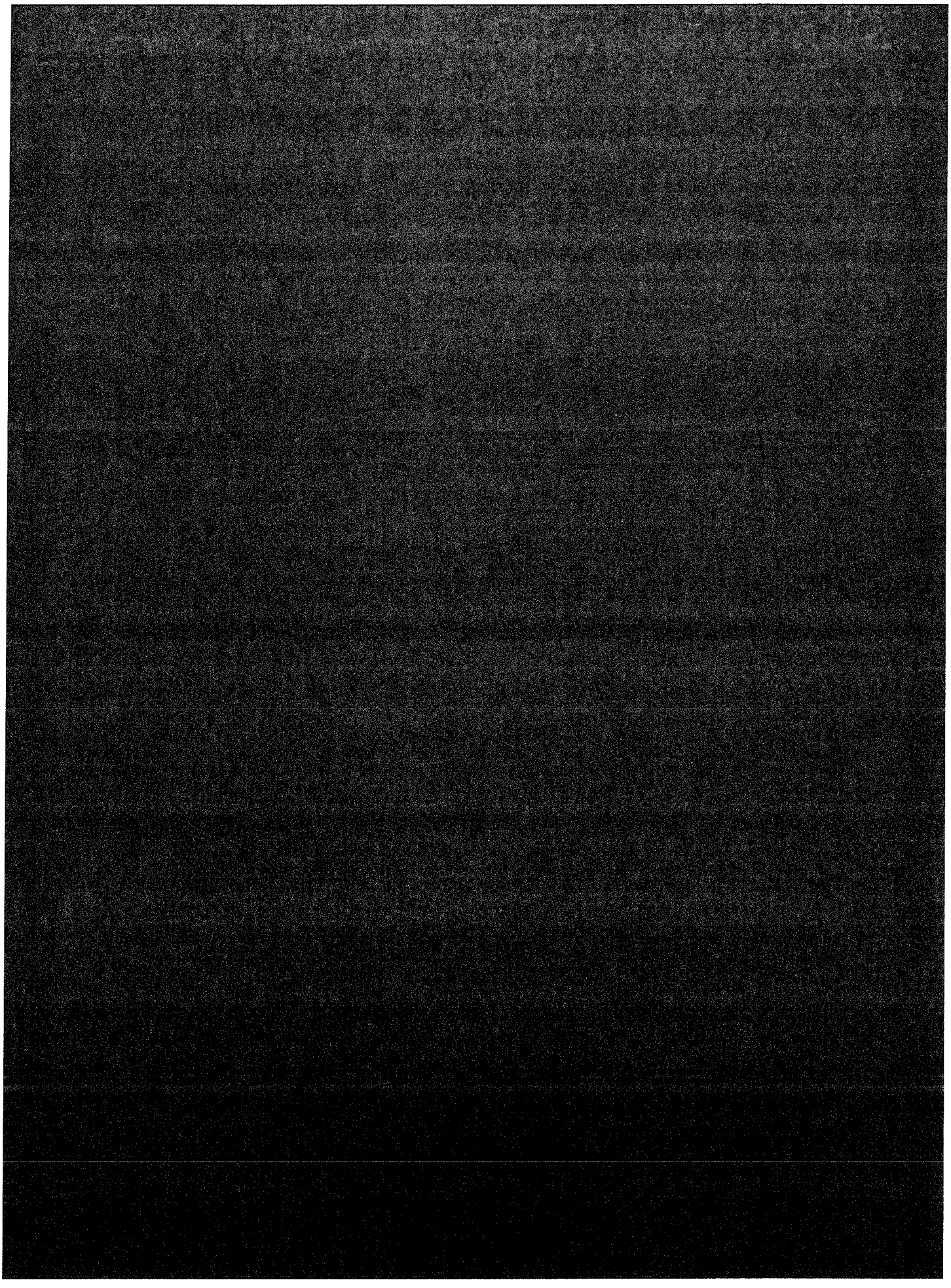


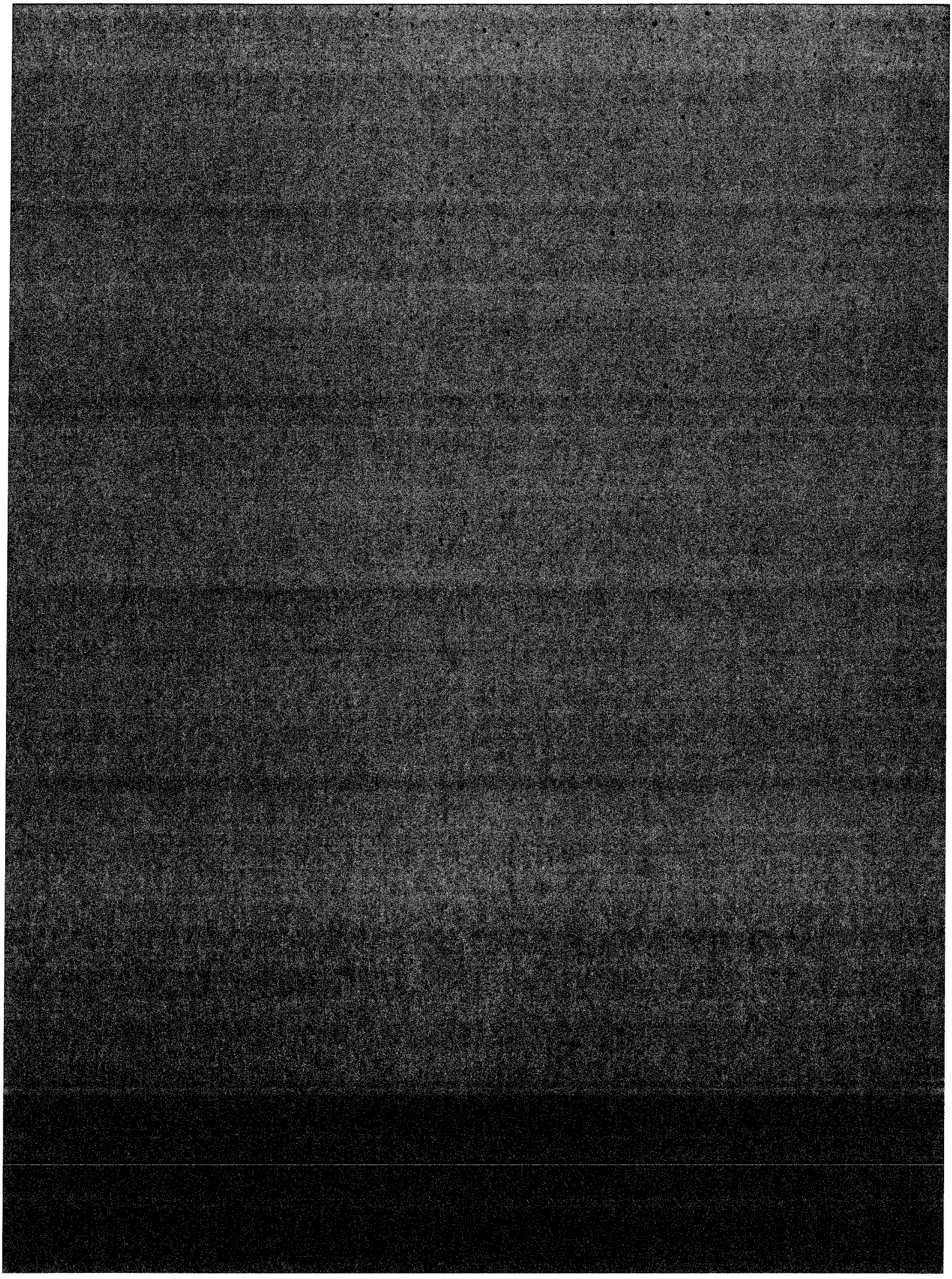
11. I declare under penalty of perjury that the foregoing is true and correct to the best of my knowledge and belief.

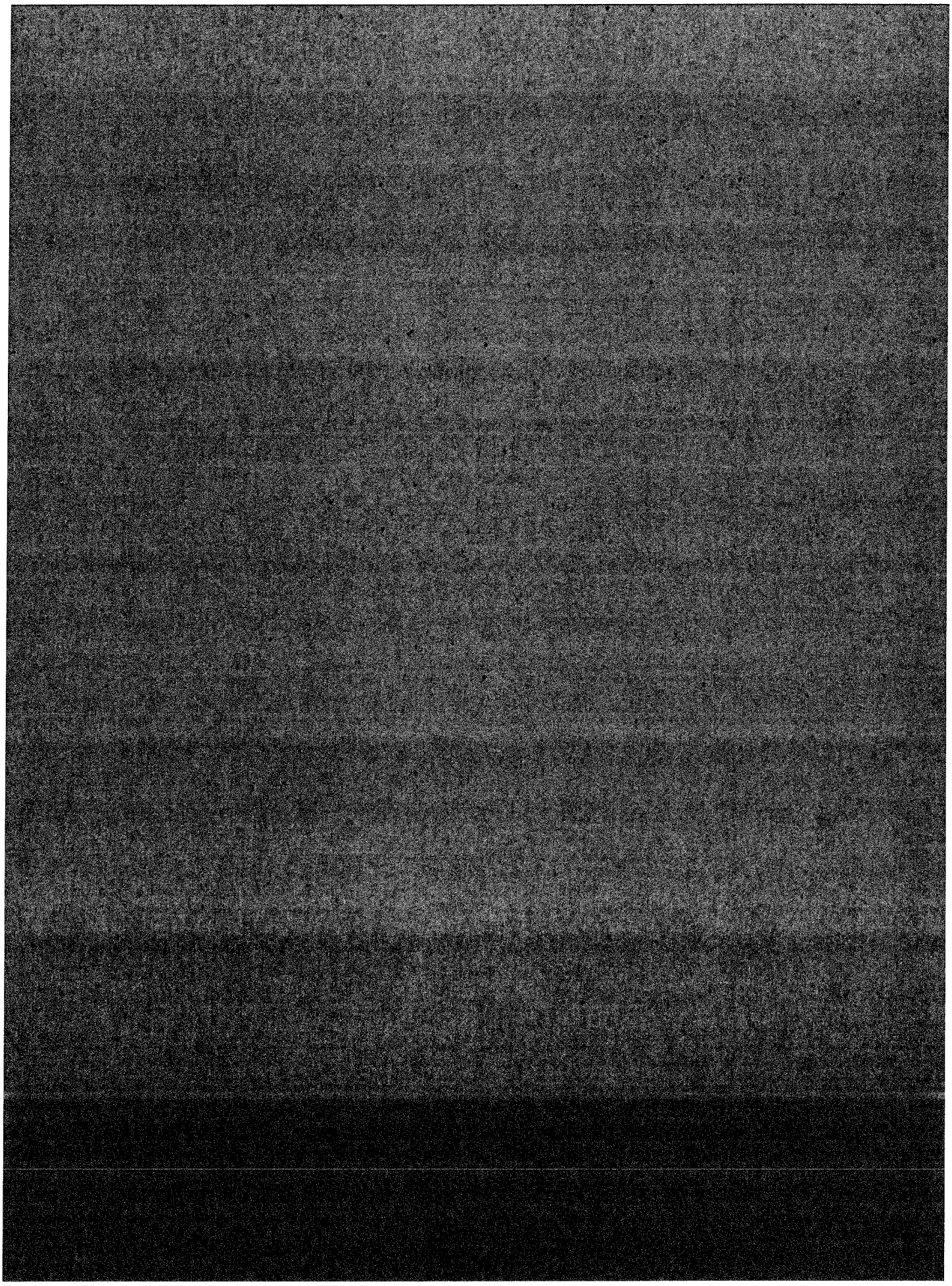
Dated: March 4, 2014
New York, NY

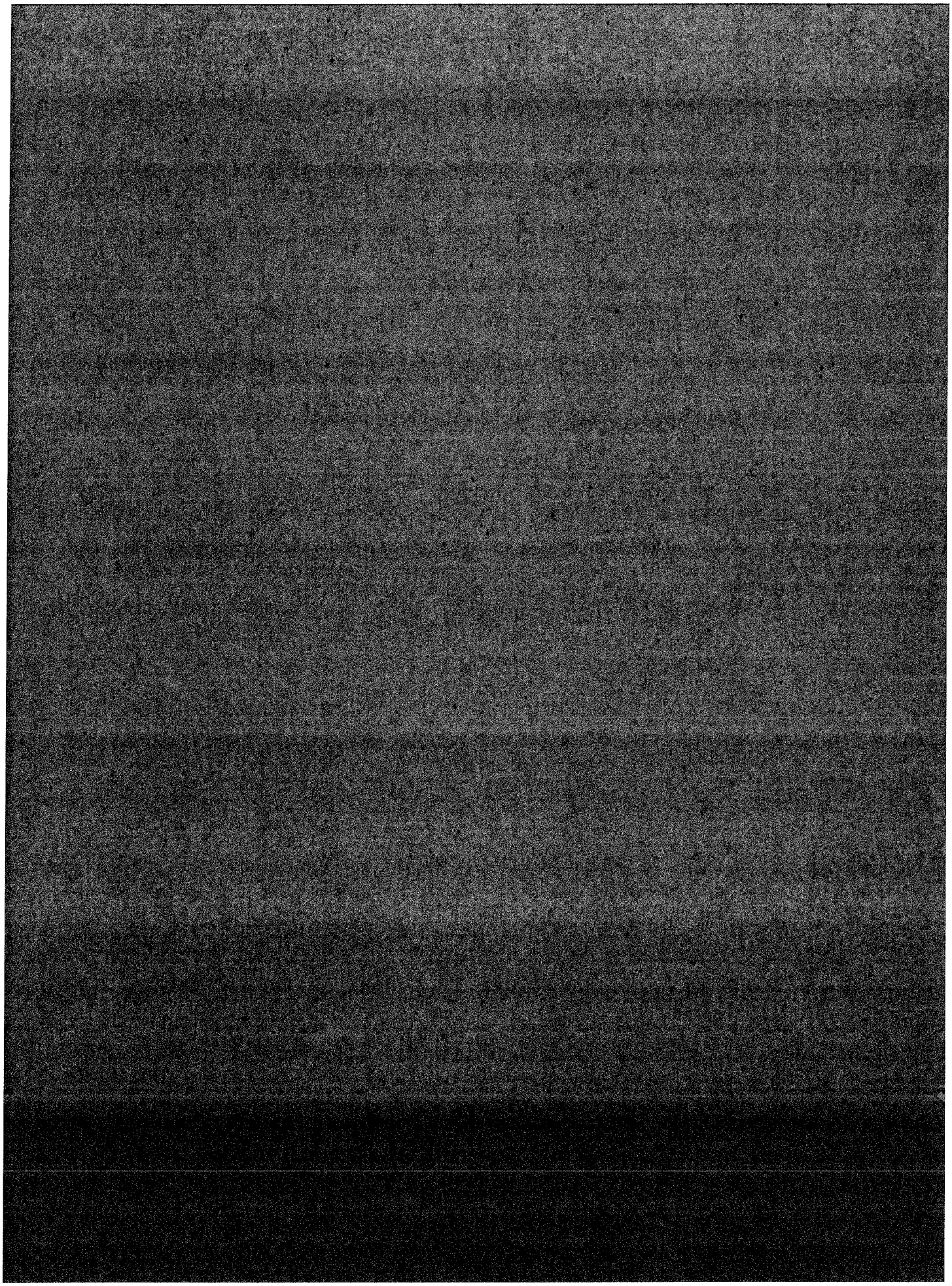
Cynthia de Luise

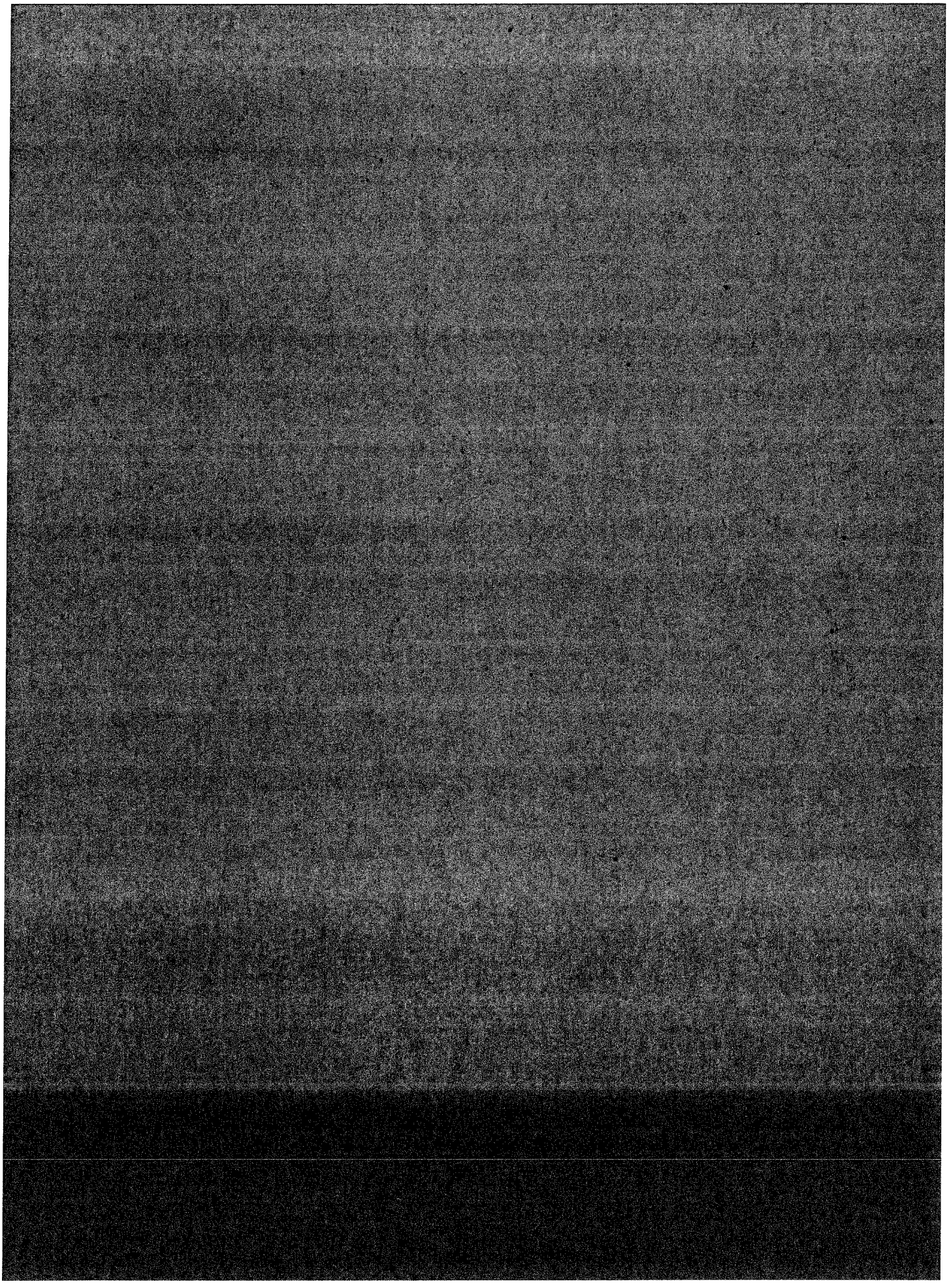
EXHIBIT A











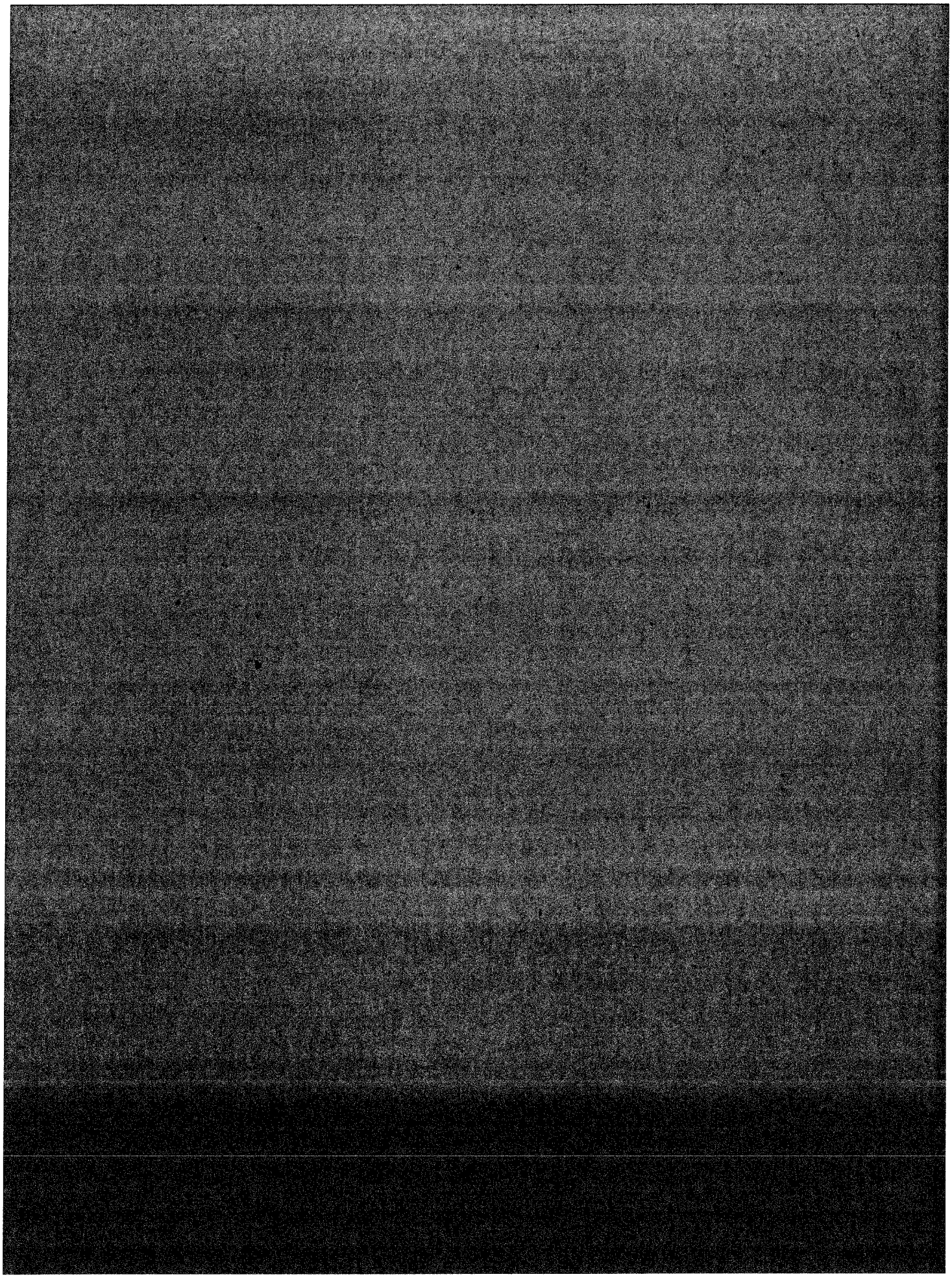


EXHIBIT B

MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
A BUSINESS UNIT OF THE MINISTRY OF HEALTH

Committees

Minutes of the 141st Medicines Adverse Reactions Committee Meeting - 11 March 2010

Updated 31 December 2012

MARC MEMBERS PRESENT

MARC SECRETARIAT PRESENT

MEDSAFE STAFF IN ATTENDANCE FOR PARTS OF THE MEETING

1 MATTERS OF ADMINISTRATION

1.1 WELCOME AND APOLOGIES

1.2 MINUTES OF THE 140TH MARC MEETING

1.3 DATES OF FUTURE MARC MEETINGS

1.4 POTENTIAL CONFLICTS OF INTEREST

1.5 PRESCRIBER UPDATE

- 1.5.1 Schedule of Planned Prescriber Update Articles
- 1.5.2 Prescriber Update. Volume 31, Number 1. February 2010

2 STANDING AGENDA ITEMS

2.1 REPORT ON STANDING AGENDA ITEMS FROM PREVIOUS MEETINGS OF THE MARC

- 2.1.1 Black cohosh, nitrofurantoin and hepatic necrosis (85273)
- 2.1.2 Methylphenidate SR (Rubifen SR) brand switch-aggressive and defiant behavioural reactions- Scheduled Review
- 2.1.3 Sodium valproate and foetal valproate syndrome, drug exposure during pregnancy (82615)
- 2.1.4 Consideration of dextropropoxyphene-containing medicines under Section 36 of the Medicines Act 1981
- 2.1.5 Drospirenone/ethinyloestradiol: risk of venous thromboembolism compared to other combined oral contraceptives
- 2.1.6 Bisphosphonates and atrial fibrillation
- 2.1.7 Cabergoline and mitral insufficiency, cardiac failure left, intestinal obstruction,

cerebral infarction [death] (85242)
2.1.8 Gabapentin and renal failure acute, hyperkalaemia, cardiac arrest (85589)
2.1.9 Sibutramine and cardiac arrhythmia [death] (85606)
2.1.10 Flutamide and hepatic failure, hepatitis (86193)
2.1.11 Digoxin and sudden death, drug level increased [death] (86454)
2.1.12 Fatalities Listing
2.1.13 Quarterly Reports from CARM
2.1.14 Pharmacovigilance issues for information only
2.1.15 The use of low-dose aspirin for primary prevention
2.1.16 Methotrexate, hydroxychloroquine, venlafaxine, and myocarditis, cardiac arrest [death] (84033)
2.1.17 Diclofenac and convulsions, numbness localised (84488)
2.1.18 Ziprasidone and arrhythmia, dyskinesia, dehydration, tremor (84310)
2.1.19 Abuse of ibuprofen/codeine combination products
2.1.20 Infanrix-hexa, Prevenar and sudden death [death] (82290)
2.1.21 Vitamin D and renal failure, hypervitaminosis D, medication error (81804)
2.1.22 Ropivacaine and convulsion grand mal, cardiac arrest, drug overdose [death] (80093)
2.1.23 SSRI antidepressants
2.1.24 Removal of specialist prescribing restriction from retinoids
2.1.25 Atorvastatin and rhabdomyolysis [death] (77591), Simvastatin and abdominal pain, rhabdomyolysis, acute renal failure, respiratory failure [death] (76185) Simvastatin and rhabdomyolysis [death] (77669) Simvastatin and rhabdomyolysis, creatine kinase increased, hepatic function abnormal, hyperkalaemia, cardiac arrest [death] (78076)
2.1.26 Lamotrigine and convulsion [death] (74826)

2.2 MEDSAFE SIGNAL DETECTION AND EVALUATION SUMMARY

3 PHARMACOVIGILANCE ISSUES

3.1 IN UTERO EXPOSURE TO SEROTONIN REUPTAKE INHIBITORS AND RISK OF CONGENITAL ABNORMALITIES

3.2 ADVERSE REACTIONS TO PIOGLITAZONE AND ROSIGLITAZONE

3.3 ORAL TERBINAFINE AND SERIOUS ADVERSE REACTIONS (BLOOD DYSCRASIAS, HEPATOTOXICITY, AND DERMATOLOGICAL REACTIONS)

3.4 STATINS, NEUROMUSCULAR DEGENERATIVE DISEASE AND AMOTROPHIC LATERAL SCLEROSIS-LIKE SYNDROME

4 MATTERS ARISING FROM THE NEW ZEALAND PHARMACOVIGILANCE CENTRE

4.1 CENTRE FOR ADVERSE REACTIONS MONITORING (CARM) SPONTANEOUS CASE REPORTS

4.1.1 Case reports

4.1.1.1 Buccaline Berna® and sudden death [death] (87419)
4.1.2 Fatalities Listing
4.1.3 Dianeal death reports
4.1.4 List reports

4.2 QUARTERLY REPORTS FROM CARM AS AT 31 DECEMBER 2009

4.3 HUMAN PAPILLOMAVIRUS VACCINE (HPV) REPORTS

5 NEW ZEALAND PHARMACOVIGILANCE-RELATED ACTIVITIES – FOR INFORMATION

6 INTERNATIONAL PHARMACOVIGILANCE-RELATED ACTIVITIES – FOR INFORMATION

6.1 AUSTRALIA

6.2 CANADA

6.3 SINGAPORE

6.4 UNITED KINGDOM

7 OTHER BUSINESS

7.1 CONTINUING MEDICAL EDUCATION

Preface:

In order to protect the privacy of those involved, descriptions of unpublished case reports are not included in these minutes.

Names of individuals have also been deleted where that person's contribution is not in the public domain, or will not shortly be so. For example, the names of those to be approached to write an article are deleted, but the names of those who have contributed to a draft article are not usually deleted. In addition, names are not usually deleted when a contribution has been made in an official capacity.

The material listed as being considered on an issue is not intended to be exhaustive.

The recommendations of the Committee are in **bold** typeface.

MINUTES OF THE 141st MEDICINES ADVERSE REACTIONS COMMITTEE MEETING

11 March 2010

The one hundred and forty-first meeting of the Medicines Adverse Reactions Committee (MARC) was held on 11 March 2010 in the Board Room, Medsafe, Wellington, New Zealand. The meeting commenced at 9.30 am and closed at 3.20 pm.

MARC MEMBERS PRESENT

Associate Professor M Rademaker (Chair)
Dr L Bryant
Professor P Ellis
Associate Professor C Frampton
Dr F McClure
Associate Professor D Reith
Dr R Savage
Dr S Sime
Dr M Tatley

MARC SECRETARIAT PRESENT

J McNee (MARC Secretary)

MEDSAFE STAFF IN ATTENDANCE FOR PARTS OF THE MEETING

A Cutfield (Advisor, Pharmacovigilance)
J Hart (Manager, Clinical Risk Management)
R Jaine (Senior Medical Advisor)
C James (Advisor, Pharmacy)
S Kenyon (Senior Advisor, Pharmacovigilance)
E Yousuf (Principal Clinical Advisor)

1. MATTERS OF ADMINISTRATION

1.1 Welcome and Apologies

The Acting Chair welcomed the attendees to the meeting. He welcomed back Dr Sime, and welcomed Dr Jaine, who was attending the meeting for the first time. Dr Jaine gave a brief synopsis of his background. Prof Ellis gave his apologies for a brief period from 1.30 to 2.30pm.

Drs Bryant, Frampton, and McClure arrived at the meeting at 9.55am due to transport difficulties, and the meeting was inquorate until this time. A summary of the discussions was provided, and the members acknowledged their agreement.

Dr Chris Cameron attended the meeting to present her paper on statins at 1.30pm.

1.2 Minutes of the 140th MARC Meeting

The minutes of the 140th meeting of the Committee were accepted as a true and accurate record of the meeting.

1.3 Dates of Future MARC Meetings

The dates for the MARC meetings for 2010 were proposed as 10 June, 9 September, and 2 December.

1.4 Potential Conflicts of Interest

Committee members submitted their Conflict of Interest Declaration forms to the Secretary. The Chair reminded the MARC members that, in addition to conflicts disclosed in the declaration forms, members should declare conflicts of interest at the commencement of discussion of any relevant agenda item.

One member declared a conflict of interest with agenda item 2.1.24. The Committee agreed it was appropriate that they be absent from the meeting during the discussion of this item.

1.5 Prescriber Update

1.5.1 Schedule of Planned *Prescriber Update* Articles

Discussion
The Committee noted the schedule of planned *Prescriber Update* articles.

1.5.2 *Prescriber Update*. Volume 31, Number 1. February 2010

Discussion
The Committee noted the latest edition of Prescriber Update.

2. STANDING AGENDA ITEMS

The Committee considered the list of issues monitored by MARC, Medsafe and NZPhvC.

2.1 Report on Standing Agenda Items from previous meetings of the MARC

Background information on these issues is available on the Medsafe web site at www.medsafe.govt.nz/profs/MARC/Minutes.asp.

2.1.1 Black cohosh, nitrofurantoin and hepatic necrosis (85273)
December 2009 minute item 2.1.9, September 2009 minute item 4.1.1.6

MARC Recommendation
In December 2010, the Committee noted the specialist advice and recommended that the Best Practice Advocacy Centre (BPAC) be asked to consider publishing an article on the treatment of recurrent urinary tract infections.

Outcome
BPAC has been asked to consider publishing an article on the treatment of recurrent urinary tract infections.

Discussion
The Committee noted the above.

2.1.2 Methylphenidate SR (Rubifen SR) brand switch-aggressive and defiant behavioural reactions- Scheduled Review
December 2010 minute item 2.1.14, September 2009 minute item 2.1.3, June 2009 minute item 2.1.5, March 2009 minute item 3.4

MARC Recommendation
In December 2010, the Committee discussed the proposed amendments to the European methylphenidate product information and recommended this information be included in the New Zealand methylphenidate data sheets.

Outcome
Medsafe has written to the sponsors for methylphenidate requesting them to update their data sheets.

Discussion
The Committee noted the above.

2.1.3 Sodium valproate and foetal valproate syndrome, drug exposure during pregnancy (82615)
December 2009 minute item 2.1.25, September 2009 minute item 2.1.20, June 2009 minute item 4.1.6.1

MARC Recommendation
In December 2009, the Committee recommended that the Precautions section of the Epilim data sheet be revised to ensure that the risk-benefit statement is clear at the beginning of the section. The Committee also recommended that the sponsor be requested to include information in the data sheet from the Meador et al paper.

Outcome
The New Zealand sponsor of Epilim has been contacted and requested to update the *Precautions* section of the data sheet to improve the clarity of the information regarding the use of sodium valproate in pregnancy.

Discussion
The Committee noted the above.

2.1.4 Consideration of dextropropoxyphene-containing medicines under Section 36 of the Medicines Act 1981
December 2009 minute item 3.1, September 2009 minute item 2.1.16, June 2009 minute item 3.2

MARC Recommendation

In December 2009, the Committee recommended that consent to distribute dextropropoxyphene-containing medicines in New Zealand be revoked.

In December 2009, the Committee recommended that Medsafe implement a transition plan for the withdrawal of dextropropoxyphene, incorporating into the plan a multi-pronged communication strategy. The Committee recommended that Medsafe inform the Committee of its transition plan at its next meeting.

Outcome

On 9 February 2010, Medsafe published a Dear Healthcare Professional letter advising of the withdrawal of dextropropoxyphene-containing medicines (included in the March 2010 dossier). This was accompanied by a media release, Question and Answer information, and the Medsafe risk-benefit review of dextropropoxyphene reviewed by the MARC at the December 2009 meeting.

Medsafe expects to confirm a final date for withdrawal shortly, following consultation with sponsors and clinicians.

Discussion

The Committee noted that following consultation with clinicians, Medsafe will provide information to prescribers regarding transferring patients to alternative treatments, both via a Dear Healthcare Professional letter and *Prescriber Update*. The Committee was advised that BPAC published a paragraph in March 2010, and agreed to include an article in a future edition of the Best Practice Journal. This article will remind GPs that dextropropoxyphene containing medicines are being withdrawn from the market and reinforce the advice already provided on alternative treatment options.

2.1.5 Drospirenone/ethinyloestradiol: risk of venous thromboembolism compared to other combined oral contraceptives
December 2009 minute item 3.2

MARC Recommendation

In December 2009, the Committee recommended that Medsafe write to the sponsor of drospirenone-containing medicines requesting that they review the risk of venous thromboembolism in association with their products (including preclinical, clinical, postmarket and observational studies) and report back to the MARC.

Outcome

The New Zealand sponsor of Yasmin and Yaz has been contacted and requested to undertake a review of the risk of VTE associated with these medicines based on data from pre-clinical studies, clinical trials, spontaneous reports and epidemiological studies. Medsafe will present the results of this review to the MARC in due course.

Discussion

The Committee noted the above.

2.1.6 Bisphosphonates and atrial fibrillation
December 2009 minute item 3.3

MARC Recommendation
In December 2009, the Committee recommended that the issue of bisphosphonates and atrial fibrillation risk be removed from the *Scheduled Review* list.

Outcome
The issue of bisphosphonates and atrial fibrillation risk has been removed from the *Scheduled Review* list.

Discussion
The Committee noted the above.

2.1.7 Cabergoline and mitral insufficiency, cardiac failure left, intestinal obstruction, cerebral infarction [death] (85242)
December 2009 minute item 4.1.1.1

MARC Recommendation
In December 2009, the Committee recommended that NZPhvC approach the appropriate specialist prescribing groups of cabergoline, advising them of this case report and requesting that members report any similar events.

Outcome
NZPhvC has written to the secretaries of the Cardiac Society of Australia and New Zealand and the New Zealand Society for Endocrinology asking them to draw the attention of members to this case report and requesting them to report to CARM any similar events especially where the total dose of cabergoline has been lower than expected for the development of cardiac valve lesions.

Discussion
The Committee noted the above.

2.1.8 Gabapentin and renal failure acute, hyperkalaemia, cardiac arrest (85589)
December 2009 minute item 4.1.1.2

MARC Recommendation
In December 2009, the Committee recommended that a *Prescriber Update* article be published to alert healthcare professionals of the risk of renal failure in association with gabapentin.

Outcome
Further information from CARM on this case report is required before a decision can be made on the content and format of an article.

Discussion

The Committee noted the above.

2.1.9 Sibutramine and cardiac arrhythmia [death] (85606)
December 2009 minute item 4.1.1.3

MARC Recommendation
In December 2009, the Committee recommended that Medsafe review the SCOUT study and the New Zealand Reductil data sheet and report back to the MARC.

Outcome
Medsafe has initiated a formal safety review of sibutramine under section 36 of the Medicines Act following the release of preliminary results from the SCOUT study and recent regulatory action in Europe.

Medsafe can only formally refer this issue to the MARC sixty days after the section 36 notice is issued; the deadline for this notice is 23 March 2010.

Medsafe will then review the data submitted in response to the section 36 notice and decide whether this issue needs to be formally referred to the MARC for consideration. If a referral is made, an out of session meeting will be organised via teleconference.

Discussion
The Committee noted that the recent additions required by the FDA to the US label for sibutramine are already contained in the NZ data sheet for Reductil, and there did not appear to be an associated risk for patients in NZ when used in accordance with the NZ data sheet. They noted that Medsafe will keep the MARC informed of the outcome of the Section 36 review.

2.1.10 Flutamide and hepatic failure, hepatitis (86193)
December 2009 minute item 4.1.1.4

MARC Recommendation
In December 2009, the Committee recommended that this case report form the basis of a *Prescriber Update* article to remind prescribers to advise patients of the possibility of flutamide causing hepatic reactions and to consult a health care professional if symptoms of hepatic dysfunction occur.

Outcome
An article entitled "Flutamide case report- serious hepatic reaction" was published in the February 2010 edition of *Prescriber Update*.

Discussion
The Committee noted the above.

2.1.11 Digoxin and sudden death, drug level increased [death] (86454)
December 2009 minute item 4.1.1.7

MARC Recommendation
In December 2009, the Committee recommended that NZPhvC request further information about this case, specifically regarding anti-psychotic medicines.

In December 2009, the Committee recommended that the Coroner be sent a copy of the NZMJ article regarding digoxin monitoring.

Outcome
The Coroner has been sent a copy of the NZMJ article regarding digoxin monitoring and has been asked to send further information regarding concurrent medications, especially antipsychotics.

Discussion
The Committee noted the above.

2.1.12 Fatalities Listing
December 2009 minute item 4.1.2

MARC Recommendation
In December 2009, the Committee recommended that further details be provided for case reports:

4.1.2.17 Sertraline (86239)

Outcome
[..]

Discussion
The Committee noted the further details provided and determined that no further action was indicated.

2.1.13 Quarterly Reports from CARM
December 2009 minute item 4.1.2

MARC Recommendation
In December 2009, the Committee recommended that NZPhvC and Medsafe review the format of the quarterly report.

Outcome
This review is ongoing.

Discussion
The Committee noted the above.

2.1.14 Pharmacovigilance issues for information only
December 2009 minute item 5

MARC Recommendation
In December 2009, the Committee recommended that the Medsafe Signal Detection and Evaluation paper be included in each agenda as an Annex to the Standing Agenda report.

Outcome
The Medsafe Signal Detection and Evaluation paper will be included in each agenda as an Annex to the Standing Agenda report.

Discussion
The Committee noted the above.

2.1.15 The use of low-dose aspirin for primary prevention
December 2009 minute item 8.1

MARC Recommendation
In December 2009, the Committee recommended that Medsafe review the recently published studies on the use of low-dose aspirin in primary prevention and report back to the MARC.

Outcome
Medsafe has reviewed the paper and considered that it did not require further action at this time.

Discussion
Medsafe advised that BPAC published an article on this topic in its December 2009 edition.

2.1.16 Methotrexate, hydroxychloroquine, venlafaxine, and myocarditis, cardiac arrest [death] (84033)
September 2009 minute item 4.1.1.2

MARC Recommendation
In September 2009, the Committee recommended that Medsafe request a review of QT prolongation in association with hydroxychloroquine from the product sponsor.

Outcome
This report was included in the March 2010 dossier.

Annexes

1. Medsafe report (2010). Drug-induced QT prolongation
2. CARM (2010). Review for MARC - March 2010. Hydroxychloroquine and Chloroquine with QT prolongation

3. Summary of post-marketing reports of QT prolongation and/or TdP received by sanofi-aventis
4. Chen C-Y et al (2006). Chronic Hydroxychloroquine Use Associated with QT prolongation and Refractory Ventricular arrhythmia. *Clinical Toxicology* 44:173-175.
5. Yanturali S et al (2004). Massive hydroxychloroquine overdose. *Acta Anaesthesiol Scand*; 48:379-381
6. Eisen A et al (2009). Arrhythmias and Conduction Defects in Rheumatological Diseases - A Comprehensive Review. *Semin Arthritis Rheum* 39:145-146.

At its December 2009 meeting, the MARC recommended a review of QT prolongation in association with hydroxychloroquine following the review of a CARM case report. The 2010 Medsafe report summarised the available data on the risk of QT prolongation and the potentially fatal ventricular arrhythmia torsades de pointes (TdP) in association with hydroxychloroquine (HCQ) therapy. The data included a review by the New Zealand sponsor of Plaquenil, a review of spontaneous reports to CARM and the WHO, and a review of published literature. Finally a comparison with chloroquine (CQ), a structurally related compound, was made.

The Committee was asked to advise whether:

- The information presented in the Medsafe report suggested that HCQ is associated with drug induced QT prolongation
- Updates to the Warnings or Adverse Effects section of the HCQ and/or CQ data sheets were warranted in light of the information presented in this report
- The results of this review be communicated in a *Prescriber Update* article.

Discussion

The Committee noted the 2010 Medsafe report.

The Committee noted that clinical studies have demonstrated that patients with autoimmune rheumatic diseases are at an increased risk of developing cardiac rhythm and conduction disorders and sudden cardiac death than the general population. The Committee noted the 2009 review by Eisen A et al, which identified one study that found that QT prolongation occurred more commonly in patients with systemic lupus erythematosus (SLE) than in healthy controls. In addition, it was noted that recent cross-sectional studies had found an association between the presence of anti-Ro/SSA antibodies and the development of QT prolongation.

The Committee noted that HCQ and CQ are both 4-aminoquinolones which differ only slightly structurally and have similar pharmacokinetic and safety profiles. A data sheet comparison showed that the overdose section of the HCQ data sheet includes class information for all 4-aminoquinolones. The CQ data sheet includes heart rhythm disorders, cardiomyopathy, and ECG changes in the adverse reactions section.

The Committee noted that the clinical overview of HCQ and QT prolongation provided by the product sponsor concluded that HCQ use was not associated with the development of QT prolongation when used in therapeutic doses. However, the sponsor stated that symptoms of HCQ overdosage may include cardiac rhythm and conduction disorders followed by sudden early respiratory and cardiac arrest and proposed to amend the Plaquenil (hydroxychloroquine)

data sheet by including QT prolongation in the Overdose section. The Committee noted the summaries of the post-marketing case reports provided by the sponsor and considered that some of these cases may have been consistent with a drug-induced QT prolongation. A literature search identified one case report which was consistent with a drug-induced QT prolongation in a patient who received HCQ 200mg for one year, ie therapeutic use of HCQ. The patient improved on dechallenge, providing further evidence for an association with HCQ use.

The Committee noted the paper by Nord et al (2004) describing two cases of HCQ associated cardiotoxicity in SLE and providing a review of the literature. The four cases of HCG associated cardiotoxicity reported in this paper did not provide direct evidence of an association with QT prolongation. However, the case descriptions of two patients described palpitations and the development of ventricular arrhythmias which may have been due to the development of QT prolongation and/or TdP. This review suggested that the cardiotoxicity associated with HCQ is similar to that reported with CQ. The Committee agreed that these cases highlight the difficulties with diagnosing drug induced QT prolongation and/or TdP in the absence of ECG recordings.

The Committee noted that there have been a number of published case reports of QT prolongation occurring in association with HCQ overdose, providing clear evidence of QT prolongation and the development of potentially fatal ventricular arrhythmias that occurs with HCQ in overdose. They noted that HCG overdose also produces a severe hypokalaemia, which may have contributed to the development of arrhythmias. The authors of the reviewed papers all noted that the features of HCQ overdose were consistent with those previously described with CQ overdose and include rapid onset of cardiovascular collapse with refractory hypotension and ventricular arrhythmias.

The Committee noted that the WHO database includes reports of QT prolongation and cardiac arrhythmias associated with both hydroxychloroquine and chloroquine. There have been published case reports supporting an increased risk of QT prolongation in association with both medicines. The Committee agreed that the absence of cases in clinical trials does not provide reassurance that HCQ is not associated with an increased risk of QT prolongation and TdP. As HCQ is an old medicine, it was approved for use prior to requirements by regulators for thorough pre-clinical and clinical QT/QTc studies to be performed, and therefore there are no available data on the effects of HCQ on cardiac potassium (HERG) channels. They noted that CQ is included on the well respected Arizona CERT website of Drugs with Risk of Torsades de Pointes maintained by the University of Arizona, and is generally accepted to be associated with an increased risk of QT prolongation and TdP.

The Committee agreed that the available evidence suggested that there is a potential risk of QT prolongation occurring in association with HCQ use, and that the greatest risk appeared to be in the overdose setting. However, they considered that patients with other risk factors for QT prolongation, particularly those with hepatic or renal disease or those with electrolyte abnormalities, may also be at an increased risk. The Committee recommended that the sponsor be required to update the Warnings section as well as the Overdose section of the Plaquenil data sheet to include information on risk of QT prolongation and/or TdP. The Committee also recommended that the CQ data sheet be similarly updated.

The Committee noted that Medsafe will continue to monitor and evaluate international regulatory activity and safety-related data as it arises. Should any further information emerge

that could significantly alter the risk-benefit balance for HCQ, this information will be presented to the MARC.

Recommendation

The Committee recommended that the sponsor be required to update the Warnings section as well as the Overdose section of the Plaquenil (hydroxychloroquine) data sheet to include information on risk of QT prolongation and/or TdP. The Committee also recommended that the CQ data sheet be similarly updated.

The Committee recommended that a *Prescriber Update* article be published on medicines which can cause QT prolongation, including reference to the Arizona CERT website.

2.1.17 Diclofenac and convulsions, numbness localised (84488) September 2009 minute item 4.1.1.3

MARC Recommendation

The Committee recommended that Medsafe request a review of the 200mg dose recommendations for diclofenac from the product sponsors.

Outcome

The possible datasheet discrepancy that has been identified relates to Voltfast Powder, which has a 200 mg/day dosage regimen for migraine. This medicine is the only approved medicine in New Zealand with this dosage for migraines, although there are other medicines with an approved dosage of 200 mg/day for primary dysmenorrhoea. This medicine was approved on the basis of clinical trial data, which included a clinical study in patients with migraine. The indications and dosing for Voltfast are consistent with the Australian Voltfast Prescribing Information.

NZPhvC has reviewed the reports in the CARM database describing acute renal failure causally assessed as being associated with diclofenac. A total of 59 such reports was identified; 5 of these reports indicated that the patient was taking >150 mg/day but not for the treatment of migraine.

It was noted that some of the reports >200mg/day are suggestive of sub-optimal prescribing and use of both prescription and OTC NSAIDs. This issue has already been highlighted in a recent *Prescriber Update* article (May 2009).

There have been no reports CARM describing serious adverse events associated with the use of diclofenac at 200 mg/day for the treatment of migraine. Therefore, at the current time, there is no basis upon which to request sponsors conduct a review.

Medsafe recommends that no further action be taken at this time. Should information become available to suggest that taking 200 mg/day of diclofenac for short durations increases the risk of acute renal failure or other serious adverse reactions, Medsafe will reconsider this issue.

Discussion

The Committee noted the above.

2.1.18 Ziprasidone and arrhythmia, dyskinesia, dehydration, tremor (84310) September 2009 minute item 4.1.1.4

MARC Recommendation

In September 2009, the Committee recommended that a *Prescriber Update* article be written reminding prescribers of the effect of antipsychotics in general on the QT interval.

Outcome

This information was included in an article entitled 'Antipsychotics and cardiac safety" published in the February 2010 edition of *Prescriber Update*.

Discussion

The Committee noted the above.

2.1.19 Abuse of ibuprofen/codeine combination products September 2009 minute item 8.1

MARC Recommendation

The Committee recommended that Medsafe obtain a copy of the recent presentation at Wellington Hospital regarding abuse of ibuprofen/codeine combinations products and determine if further action is required.

Outcome

Medsafe has been unable to obtain a copy of this presentation.

At its November 2009 meeting, the Medicines Classification Committee (MCC) discussed whether access to codeine should be further restricted, and whether pack sizes should be limited, in combination products containing increasingly larger doses of codeine.

The MCC agreed to reclassify codeine in combination products as a restricted medicine when:

- each dose unit contains not more than 15 mg of codeine base
- the maximum daily dose is limited to 100 mg of codeine base
- the pack size is not more than five days' supply
- sold in packs approved by the Minister or the Director-General for distribution as a restricted medicine.

The Committee also concluded that cough and cold preparations containing codeine could be classified as pharmacy-only medicines when:

- each dose unit contains not more than 15 mg of codeine base
- the maximum daily dose is limited to 100 mg of codeine base
- the pack size is not more than six days' supply
- sold in packs approved by the Minister or the Director-General for distribution as a pharmacy-only medicine.

The Committee noted these recommendations could create the situation where those addicted to codeine may try to seek alternative sources of codeine from cough and cold medicines.

Following discussion the MCC agreed that the decision to allow cough and cold preparations containing codeine to continue to be available at the pharmacy-only level should be reviewed in 12-18 months time. In the interim the Committee recommended that Medsafe should write to the Pharmaceutical Society and the Pharmacy Guild explaining that, following the reclassification of codeine in combination analgesic products as restricted medicines, the risk of patients addicted to codeine transferring from analgesics to the cough and cold preparations containing codeine could increase. The letter should request the Pharmacy sector to treat codeine containing cough and cold medicines as potentially addictive medicines and, in keeping with the Pharmacy Council Code of Ethics, require these products be moved behind the counter and not be available for self selection. The letter would also ask pharmacists to warn patients about the risk of addiction to cough and cold preparations. The Committee finally suggested that Medsafe should publish an article on the reclassification of codeine for General Practitioners and pharmacists in *Prescriber Update*. The article should also advise prescribers and pharmacists to warn patients about the risks of addiction to codeine.

The Committee also discussed the United Kingdom's decision to label codeine containing products with warning statements regarding addiction. The Committee supported the United Kingdom's approach and felt it would further discourage long term use of these products.

Discussion
The Committee questioned the details of the reclassification, and Medsafe agreed to provide clarification.

2.1.20 Infanrix-hexa, Prevenar and sudden death [death] (82290)
September 2009 minute item 2.1.5, June 2009 minute item 2.1.9, March 2009 minute item 4.1.1.9

MARC Recommendation
In March 2009 the Committee recommended that NZPhvC bring further information to the MARC when the Coroner's report has been received.

Outcome
The NZPhvC will bring back any further information to the MARC when received.

Discussion
The Committee noted the above.

2.1.21 Vitamin D and renal failure, hypervitaminosis D, medication error (81804)
September 2009 minute item 2.1.8, June 2009 minute item 2.1.12, March 2009 minute item 4.1.4.1

MARC Recommendation
In March 2009 the Committee recommended that this event be followed up through Medsafe.

Outcome
Medsafe has begun the follow up process and will inform the MARC of the outcome.

Discussion
The Committee noted the above.

2.1.22 Ropivacaine and convulsion grand mal, cardiac arrest, drug overdose [death] (80093)
September 2009 minute item 2.1.11, June 2009 minute item 2.1.18, March 2009 minute item 2.1.7, December 2008 minute item 4.1.1.1

MARC Recommendation
In December 2008 the Committee recommended that NZPhvC provide a follow-up report to the MARC when the Coroner's report has been received.

Outcome
The Coroners report has still not yet been received by CARM.

Discussion
The Committee noted the above.

2.1.23 SSRI antidepressants
September 2009 minute item 2.1.12, June 2009 minute item 2.1.10, March 2009 minute item 2.1.12, December 2008 minute item 9.2

MARC Recommendation
In December 2008 the Committee recommended that a formal request be made to the Coroner's Office to forward the decisions relating to medication related cases directly to the NZPhvC.

Outcome
The Waikato Coroner has agreed to forward his decisions related to medication-related cases to the MARC and NZPhvC.

A similar request will be made to the other Coroner's Offices throughout the country.

Discussion
The Committee noted the above.

2.1.24 Removal of specialist prescribing restriction from retinoids
June 2009 minute item 2.1.21, March 2009 minute item 2.1.13, December 2008 minute item 9.4

MARC Recommendation
In December 2010, the Committee noted that a formal Risk Management Plan is expected to be submitted by the New Zealand sponsor of Oratane (isotretinoin) shortly.

Medsafe will provide details of the Risk Management Plans to the MARC when available.

Associate Professor Rademaker was not present during the discussion of this agenda item.

Outcome
This report was included in the March 2010 dossier.

Discussion
The Committee noted the 2010 Medsafe report.

The Committee noted the description of risk mitigating strategies in place to minimise the incidence of pregnancy exposure to isotretinoin provided by Douglas Pharmaceuticals, the product sponsor.

The Committee was updated on the usage data, which indicated that there has been no increase in prescribing of isotretinoin since access to funded isotretinoin was widenened in March 2009,

The Committee noted that the frequency of adverse reaction reports received annually has not changed significantly over the last ten years. One report of unintended pregnancy was received prior to the widening of access to funded isotretinoin in New Zealand.

A member commented that the resources for patients and healthcare professionals did not appear to be easily obtained. The Committee considered that these resources were an important component of the risk management plan, and suggested that Medsafe work in conjunction with PHARMAC to increase availability of these resources.

The Committee agreed that the risk minimisation plan proposed by Douglas Pharmaceuticals appears adequate at this time. They noted that the proposal to develop a patient database involved many complexities and would be of limited value at present. They noted that the Consumer Medicine Information (CMI) has not been updated since 2006, and recommended that Medsafe request the sponsor to provide an updated CMI for isotretinoin, highlighting the need to avoid pregnancy while taking this medicine.

Medsafe will continue to monitor adverse reaction reports received for isotretinoin and will request an annual Periodic Safety Update Review (PSUR) be provided by the product sponsor. Medsafe will require that the PSUR includes a description of all adverse reaction reports submitted in New Zealand, including those submitted to CARM.

Recommendation
The Committee recommended that Medsafe request the sponsor to provide an updated CMI for isotretinoin, further highlighting the need to avoid pregnancy while taking this medicine.

2.1.25 Atorvastatin and rhabdomyolysis [death] (77591), Simvastatin and abdominal pain, rhabdomyolysis, acute renal failure, respiratory failure [death] (76185) Simvastatin and rhabdomyolysis [death] (77669) Simvastatin and rhabdomyolysis, creatine kinase increased, hepatic function abnormal, hyperkalaemia, cardiac arrest [death] (78076) September 2009 minute item 2.1.23, June 2009 minute item 2.1.29, March 2009 minute

item 2.1.22, December 2008 minute item 2.1.12, September 2008 minute item 2.1.8, May 2008 minute items 4.1.1.3, 4.1.1.4, 4.1.1.5, 4.1.1.6

MARC Recommendation
In September 2009, the Committee recommended that Dr Cameron be invited to the December meeting of the MARC to present her report on statins and dose response data.

Outcome
Dr Cameron presented her report at the March 2010 meeting of the MARC.

2.1.26 Lamotrigine and convulsion [death] (74826)
September 2009 minute item 2.1.24, June 2009 minute item 2.1.31, March 2009 minute item 2.1.21, December 2008 minute item 2.1.21, September 2008 minute item 2.1.21, May 2008 minute item 2.1.14, March 2008 minute item 2.1.18, December 2007 minute item 2.1.17, September 2007 minute item 2.1.9, June 2007 minute item 4.1.1.3

MARC Recommendation
In June 2007, the Committee recommended that NZPhvC should provide a follow up report to the MARC when the Coroner's report or further information that facilitates assessment becomes available.

Outcome
The Coroner's report is still outstanding; however, a follow-up response provided details from the post mortem. This report states that in the pathologist's opinion, "the cause of death was probably related to an epileptic convulsion in view of the hyper-expanded lungs and lack of other pathology found or abnormal toxicology".

Discussion
The Committee noted the above.

2.2 Medsafe Signal Detection and Evaluation summary

The Committee noted the February 2010 Medsafe report. They noted Medsafe has reviewed hypersensitivity syndrome in association with anticonvulsants and suggested that a *Prescriber Update* article be published around this topic.

Recommendation
The Committee recommended that a *Prescriber Update* article be considered around the topic of hypersensitivity syndrome in association with anticonvulsants.

3. PHARMACOVIGILANCE ISSUES

3.1 In Utero Exposure To Serotonin Reuptake Inhibitors And Risk Of Congenital Abnormalities

References

1. Summary of cases reported to CARM.
2. Tuccori M, Testi A, Antonioli L, et al 2009. 'Safety concerns associated with the use of serotonin reuptake inhibitors and other serotonergic/noradrenergic antidepressants during pregnancy: a review' *Clinical Therapeutics* **31**: 1426-1453.
3. Pederson LH, Henriksen TB, Vestergaard M, et al 2009 'Selective serotonin reuptake inhibitors in pregnancy and congenital malformation: population based cohort study; **339**: b3569
4. Merlob P, Birk E, Sirota L, et al 2009 'Are selective serotonin reuptake inhibitors cardiac teratogens? Echocardiographic screening of newborns with persistent heart murmur' *Birth Defects Res (A)*; **85**: 837-841.
5. Wurst KE, Poole C, Ephross SA et al 2009 'First trimester paroxetine use and the prevalence of congenital, specifically cardiac defects: a meta-analysis of epidemiological studies'. Birth Defects Res Part A Clin Mol Teratol Sept [Epub ahead of print].
6. Wichman CL, Moore KM, Lang TR, et al 2009 'Congenital Heart Disease Associated with selective serotonin Reuptake Inhibitor Use in Pregnancy' *May Clin Proc*; **84**: 23-27.
7. Diav-Citrin O, Shectman S, Weinbaum D, et al 2009 'Paroxetine and fluoxetine in pregnancy: a prospective, multicentre, controlled, observational study' *Br J Clin Pharmacol*; **66**: 695-705.
8. Extract from the report of the psychiatric drug safety expert advisory panel 2009 Therapeutic Drugs Administration. http://www.tga.gov.au/alerts/medicines/pdseap-report2009.htm
9. Summary of cases reported to CARM.
10. Tuccori M, Testi A, Antonioli L, et al 2009. 'Safety concerns associated with the use of serotonin reuptake inhibitors and other serotonergic/noradrenergic antidepressants during pregnancy: a review' *Clinical Therapeutics* **31**: 1426-1453.
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14. Wichman CL, Moore KM, Lang TR, et al 2009 'Congenital Heart Disease Associated with selective serotonin Reuptake Inhibitor Use in Pregnancy' *May Clin Proc*; **84**: 23-27.
15. Diav-Citrin O, Shectman S, Weinbaum D, et al 2009 'Paroxetine and fluoxetine in pregnancy: a prospective, multicentre, controlled, observational study' *Br J Clin Pharmacol*; **66**: 695-705.
16. Extract from the report of the psychiatric drug safety expert advisory panel 2009 Therapeutic Drugs Administration. http://www.tga.gov.au/alerts/medicines/pdseap-report2009.htm

Background

Medsafe provided a report on the issue of in utero exposure to serotonin reuptake inhibitors (SSRIs and SNRIs) and risk of congenital abnormalities following the recent publication of a number of new epidemiological studies.

The MARC has previously reviewed the use of SSRIs in pregnancy. Studies investigating the risk of congenital malformations included in the previous reviews were:

- Louik et al 2007 *NEJM* 356 2675-83.
- Alwan et al 2007 *NEJM* 356 2684-92.
- Wogelius et al 2006 *Epidemiology* 17 701-4.
- Kallen B 2006 *Reproductive Toxicol* 3 221-2.
- Cole JA et al 2005 Preliminary report for GSK .
- Hallberg P et al 2005 *J Clin Psychopharm*. 25 59-73.
- Ericson A et al 1999 *Eur J Clin Pharmacol* 55: 503-508.

A *Prescriber Update* article on SSRI use in pregnancy was published in June 2008.

Discussion

The Committee noted the 2010 Medsafe report.

Medsafe advised that in March 2010 the MHRA advised that there appears to be a small increased risk of congenital cardiac defects in association with fluoxetine in early pregnancy, similar to that seen with paroxetine.

The Committee noted that untreated antenatal depression has been associated with adverse foetal outcomes including congenital defects. These risks need to be considered when reviewing the benefits and risks of medicinal treatment for depression in pregnancy.

The Committee considered that there were problems interpreting the published epidemiological studies. All the reported studies were conducted differently making a consistent outcome hard to determine. Whilst some studies appear to have shown risks of particular congenital anomalies with different medicines, there did not appear to be enough evidence to warrant including a strong statement in the product data sheets at the present time, with the exception of fluoxetine and paroxetine (a statement is already included in the paroxetine data sheet).

The Committee noted that the need for treatment should be made on an individual patient basis. Whilst it may be preferable to try non-pharmacological intervention, this should be balanced against the risk of relapse and of adverse foetal outcomes associated with

depression of the mother. The Committee noted that there did not appear to be any evidence to show that any SSRI may be safer and that the risk in association with tricyclic antidepressants was unknown.

The Committee did consider that the results of the recent studies justified including a more general warning in the data sheets around the risk of congenital anomalies found in epidemiological studies in association with SSRI/SNRI treatment.

Recommendation

The Committee recommended that sponsors for fluoxetine medicines be requested to update their data sheets regarding the risk of congenital anomalies when used in pregnancy. The Committee recommended that sponsors for relevant medicines other than fluoxetine and paroxetine be requested to add a general warning to the data sheets stating that there may be an increased risk of congenital abnormalities associated with SSRI (SNRI) treatment in pregnancy. The Committee recommended that a *Prescriber Update* article be written on this issue.

3.2 Adverse Reactions To Pioglitazone And Rosiglitazone

References

1. Dormandy J, Bhattacharya M, van Troostenburg de Bruyn AR 2009 'Safety and tolerability of pioglitazone in high risk patients with type 2 diabetes. An overview of data from PROactive' *Drug Safety* 2009 32: 187-202.
2. Mannucci E, Monami M, Di Bari M et al 2009 'Cardiac safety profile of rosiglitazone-A comprehensive meta-analysis of randomized clinical trials' *Int J Cardiol* doi:10.1016/j.ijcard.2009.01.064
3. Home PD, Pocock SJ, Nielsen et al 2009 'Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open label trial' *Lancet* 373: 2125-35
4. Juurlink DN, Gomes T, Lipscome LL et al 2009 'Adverse cardiovascular events during treatment with pioglitazone: population based cohort study' *BMJ* 339: b2942.
5. Bodmer M, Meier C, Kraenzlin ME et al 2009 'Risk of fractures with Glitazones. A critical review of the evidence to date' *Drug Safety* 32: 539-547.
6. Floyd JS, Barbehenn E, Lurie P et al 2009 'Case series of liver failure associated with rosiglitazone and pioglitazone' *Pharmacoepi Drug Safety* 18: 1238-1243.

Issue

The glitazones were placed on the active monitoring list for annual review in March 2006. In 2007, regulatory action was taken and data sheet updates were made. A *Prescriber Update* article on fluid retention, heart failure and macular oedema with glitazones was published in November 2007.

The purpose of this report was to update the Committee on regulatory actions and new published information from the previous 12 months.

The Committee was asked to advise whether:

- the information provided changed the safety profile for rosiglitazone and pioglitazone
- the information presented warranted any further regulatory action by Medsafe
- pioglitazone and rosiglitazone should be removed from Scheduled Review
- pioglitazone and rosiglitazone should be removed from the list of adverse reactions of current concern.

Discussion

The Committee noted the 2010 Medsafe report, which included a summary of relevant published literature (including the above references), information from Periodic Safety Update Reviews and actions taken by other medicines regulators.

The Committee considered the evidence of adverse cardiovascular outcomes and mortality. In this respect the evidence appeared to be more favourable for pioglitazone.

The Committee noted that the studies investigating cardiovascular outcomes, in general, confirmed an increased risk of heart failure with thiazolidinediones (TZDs). They noted that there was no consistent finding of an increased risk of other cardiovascular outcomes. The Committee agreed that most of the studies seemed to indicate that pioglitazone may have a more favourable cardiovascular safety profile than rosiglitazone.

The Committee noted that a review of published papers investigating the risk of fracture with TZD treatment confirmed an increase in fracture risk, which may be higher with pioglitazone treatment compared to rosiglitazone.

The Committee noted that the studies investigating renal and hepatic function appeared to indicate that TZD treatment may have beneficial effects.

The Committee noted that pioglitazone is the medicine currently funded in New Zealand, and that the number of patients currently receiving pioglitazone in New Zealand was low. The number of spontaneous reports of suspected adverse events received by CARM was also provided in the CARM quarterly report; the number of reports is very low.

The Committee noted that this Scheduled Review did not identify any new safety concerns and agreed that no regulatory action was required at the present time as a result of the review. They noted that the FDA is currently reviewing the safety of rosiglitazone and a report is expected in August. The Committee decided that significant concerns regarding rosiglitazone remained, and recommended that Medsafe report back to the MARC with the outcome of the FDA review, and include New Zealand usage data.

The Committee recommended that pioglitazone and rosiglitazone remain on the Scheduled Review and the list of adverse reactions of current concern (ARCC).

Recommendation

The Committee recommended that Medsafe report back to the MARC with the outcome of the FDA review, and include New Zealand usage data.

The Committee recommended that pioglitazone and rosiglitazone remain on the scheduled review list and the list of adverse reactions of current concern.

3.3 Oral Terbinafine And Serious Adverse Reactions (Blood Dyscrasias, Hepatotoxicity, And Dermatological Reactions)

References

1. Cumulative Summary Tabulations from Lamisil Periodic Safety Update Review (PSUR)

    - Blood and lymphatic system disorders
    - Hepatobiliary disorders
    - Skin and subcutaneous tissue disorders

2. Current New Zealand data sheet for Apo-Terbinafine

Issue

Medsafe provided a report for the MARC on serious adverse reactions associated with oral terbinafine, with a particular focus on blood dyscrasias, hepatotoxicity and dermatological reactions.

This topic was placed on the active monitoring list in September 2006 following regulatory action in Australia regarding the risk of agranulocytosis. The Committee recommended that Medsafe monitor regulatory action in Australia following a review of the safety of oral terbinafine by the Australian TGA and ensure that the New Zealand data sheets remain consistent with the Australian prescribing information.

An article advising prescribers of serious adverse reactions associated with oral terbinafine and encouraging appropriate use of the medicine was included in the November 2006 edition of *Prescriber Update.* Similar advice was also issued to pharmacists in September 2007 through the Pharmaceutical Society.

The purpose of this report was to update the Committee on any recent international regulatory action and any new published information regarding adverse reactions that have arisen since the last review of this issue in December 2008. The Committee was asked to advise whether this issue can be removed from the Scheduled Review list.

Discussion

The Committee noted the 2010 Medsafe report.

Medsafe advised that the TGA has completed its review, and that the New Zealand data sheet for Apo-Terbinafine (funded brand) remains consistent with the Australian product information with regard to serious haematological, hepatic and dermatological adverse effects.

A review of the PSUR for Lamisil (innovator brand) did not raise any safety concerns in addition to those already identified by the MARC. Several reactions were noted as being associated with terbinafine. The company is considering the inclusion of the following in the company core data sheet:

- Rhabdomyloysis and creatine phosphokinase (CPK) increase
- Permanent anosmia and other effects on the sense of smell

- Anaphylaxis, serum sickness-like reaction, vasculitis, influenza-like illness, pyrexia
- Pancreatitis
- Anaemia

The Committee agreed that Medsafe request the above updates to the New Zealand data sheets for oral terbinafine. They noted that the companies are actively monitoring a number of serious dermatological adverse effects, including drug rash with eosinophilia and systemic symptoms (DRESS syndrome), acute febrile neutrophilic dermatosis (Sweet's syndrome), and dermatomyositis.

The Committee noted that a search of the literature published since the last scheduled review of terbinafine did not identify any studies relevant to the adverse reactions of interest to the MARC containing important safety findings.

The Committee agreed that this scheduled review did not identify any safety concerns that would significantly alter the risk-benefit profile. The safety concerns with terbinafine previously raised by the MARC are adequately described in the data sheets.

The Committee noted that no significant new safety concerns have arisen since the issue was placed on the Scheduled Review list in 2006. They considered that there remains a clinical need for terbinafine in treating serious fungal infections and fungal infections in paediatric patients where alternatives are limited.

Continued monitoring and evaluation of the risk-benefit profile for terbinafine remains important, however the Committee considered it no longer required specific annual review and recommended it be removed from the Scheduled Review list.

The Committee noted that Medsafe will continue to monitor and evaluate international regulatory activity and safety-related data as it arises. Should any further information emerge that could significantly alter the risk-benefit balance for terbinafine, this information will be presented to the MARC.

Recommendation

The Committee agreed that Medsafe request the following updates to the New Zealand data sheets for oral terbinafine:

- **Rhabdomyloysis and creatine phosphokinase (CPK) increase**
- **Permanent anosmia and other effects on the sense of smell**
- **Anaphylaxis, serum sickness-like reaction, vasculitis, influenza-like illness, pyrexia**
- **Pancreatitis**
- **Anaemia.**

The Committee recommended that the issue of oral terbinafine and serious adverse reactions be removed from the Scheduled Review list.

3.4 Statins, Neuromuscular Degenerative Disease And Amotrophic Lateral Sclerosis-Like Syndrome

1. National Institute of Neurological Disorders and Stroke - Amyotrophic Lateral Sclerosis Fact Sheet.
2. Sørensen and Lash. (2009). Statins and amyotrophic lateral sclerosis - the level of evidence for an association. *Journal of Internal Medicine.* 266**:** 520-526.

Issue

Medsafe provided a report for the MARC on statins and neuromuscular degenerative disease and an amyotrophic lateral sclerosis (ALS)-like syndrome.

This issue was placed on the Scheduled Review list in September 2007, following the publication of a paper from the WHO Uppsala Monitoring Centre in *Drug Safety* which identified a possible signal of a neuromuscular adverse event associated with statin use - the development of an ALS-like syndrome.

At its review in December 2008, the MARC considered there to be insufficient evidence to warrant a change to the prescribing and use of statins with regard to the risk of ALS-like syndrome at that time. They noted that a case-control or epidemiological study was underway investigating whether statins increase the risk of developing ALS or influence progression in those who already have this disease. The Committee agreed to await the results of this study and recommended that the issue of statins and neuromuscular degenerative disease and an ALS-like syndrome remain on the Scheduled Review list.

The purpose of the 2010 review was to update the Committee on any recent data and regulatory action regarding this potential signal.

Discussion

The Committee noted the 2010 Medsafe report.

Medsafe advised that it had not been able to source the findings of the study noted at the December 2008 meeting. It was suggested that either the results have not yet been published or the study has been postponed.

The Committee noted that a literature review had identified one relevant publication relating to statins and ALS published since the last review of this issue by the MARC. The authors of this paper concluded that, at that time, there was little valid evidence that statin medications increase the risk of ALS occurrence.

The Committee agreed that based on the available data, the association between statin use and the development of an ALS-like syndrome remains unclear. However, they considered that even if an association is confirmed, the benefit-risk profile of statins remains favourable, as these medicines substantially reduce the incidence of cardiovascular morbidity, cardiovascular mortality and medical intervention associated with high cholesterol.

The Committee noted that this Scheduled Review had not identified any new evidence to warrant a change to the prescribing and use of statins with regard to the risk of an ALS-like syndrome. They considered that this issue no longer required specific annual review by the MARC and recommended it be removed from the list for Scheduled Review.

They noted that Medsafe will continue to monitor and evaluate international regulatory activity and safety-related data as it arises, including the epidemiological study that the Committee was awaiting. Should any further information emerge that could significantly alter the risk-benefit balance for statins with regard to the development of an ALS-like syndrome, this information will be presented to the MARC.

Recommendation

The Committee recommended that the issue of statins and neuromuscular degenerative disease and an ALS-like syndrome be removed from the Scheduled Review list.

4 MATTERS ARISING FROM THE NEW ZEALAND PHARMACOVIGILANCE CENTRE

4.1 Centre for Adverse Reactions Monitoring (CARM) Spontaneous Case Reports

Spontaneous reporting programme
All spontaneous reports presented at the MARC meeting have been assessed by the Centre for Adverse Reactions Monitoring (CARM) and responses have been sent to the reporters. The purpose of these responses is to assist the practitioner to discharge his/her responsibility to patients. These individual replies include as appropriate:

- comment about causality;
- information about similar suspected adverse reactions reported with the same or related medicines;
- prescribing advice;
- advice related to the care of the patient, including information that may assist the practitioner to make a risk:benefit assessment for future treatment; and
- any specific action being taken by the Centre, including entering the reaction into the National Health Index against the patient's name, presenting the case report to the MARC, etc.

Note: In the discussion notes for each report, the case has been given a causality designation using terms and definitions developed by the World Health Organisation. The precise definitions are available on the website of the The Uppsala Monitoring Centre, which is the WHO Collaborating Centre for International Drug Monitoring - http://www.who-umc.org/

These designations (certain, probable, possible, unlikely, unclassified and unclassifiable) refer to the degree of certainty about the relationship between the medicine and the adverse event. The terms should not be understood literally. For example, "certain" means that the appropriate elements are present to match the international definition. It does not mean there is absolute certainty that the medicine caused the adverse event. Explanations of these terms can be found on the Medsafe website via the hyperlink at each causality designation.

The Committee was advised that the way in which the spontaneous case reports were presented to the MARC had been refined, with the focus of cases presented to the Committee

being on advice and signal detection. The remainder of case reports are included as list reports, with an expanded section for relevant comments.

4.1.1 Case reports

4.1.1.1 Buccaline Berna® and sudden death [death] (87419)

Discussion

NZPhvC advised that the CARM database includes four reports of adverse reactions in association with Buccaline Berna®, and these are the only reports for this product in the WHO database. No information was found in the literature on adverse reactions.

The causal association with Buccaline Berna® was considered to be 'unclassified' for sudden death.

4.1.1.2 Buccaline Berna® and myocarditis [death] (87669)

Discussion

See minute item 4.1.1.1,

The causal association with Buccaline Berna® was considered to be 'unclassified' for myocarditis.

4.1.1.3 Gabapentin and encephalopathy, dysphagia, twitching, hepatic function abnormal, myocardial infarction [death] (87914)

Discussion

NZPhvC advised that the CARM database includes reports of hepatic function abnormal, twitching, and myocardial infarction. Hepatic enzymes increased have a borderline positive IC value in the WHO database, and the IC values are positive for encephalopathy and muscle contraction involuntary. The IC value for myocardial infarction in association with gabapentin is negative.

The data sheet for Neurontin (gabapentin) includes the reactions listed above, with the exception of encephalopathy and myocardial infarction.

The Committee noted that this was a complex case and the patient had significant medical history, including impaired renal function.

The causal association with gabapentin was considered to be 'probable' for encephalopathy, dysphagia, twitching, 'possible' for hepatic function abnormal, and 'unlikely' for myocardial infarction.

4.1.1.4 Paracetamol and liver failure, overdose, medication error [death] (87812)

Discussion

NZPhvC advised that two previous reports had been received of medication error in combining over-the-counter and prescribed nonsteroidal anti-inflammatory drugs.

The Committee agreed that communicating messages to the public regarding the risks of self-medication was of on-going concern and remained a challenge.

The Committee considered the causal association with paracetamol to be 'probable' for liver failure, overdose and medication error.

4.1.1.5 HPV, medroxyprogesterone and paraesthesia, cognition abnormal, muscle weakness, night sweats, sudden death [death] (87237)

Discussion

NZPhvC advised that there are no other reports of death in association with HPV in the CARM database.

The Committee noted that this is an interim report as the cause of death is under Coronial Review. They agreed that the autopsy and Coronial findings will provide a basis from which to more adequately evaluate this case, and recommended that NZPhvC report back to the MARC when this information is available.

The Committee considered the causal association with HPV, medroxyprogesterone was 'unclassifiable' for paraesthesia, cognition abnormal, muscle weakness, night sweats, sudden death.

Recommendation

The Committee recommended that NZPhvC report back to the MARC when the autopsy and Coronial findings are available.

4.1.1.6 Infanrix Hexa, Prevenar and Sudden Infant Death Syndrome [death] (87446)

Discussion

The Committee considered the causal association with Infanrix Hexa, Prevenar to be 'unlikely' for sudden infant death syndrome.

4.1.1.7 Omeprazole and hypomagnesaemia, hypocalcaemia (86867)

Discussion

The Committee noted that two CARM case reports of hypomagnesaemia and hypocalcaemia had been reviewed by the MARC at the September 2008 meeting, when it was considered that there was not yet enough evidence for regulatory action.

In the WHO database, both hypomagnesaemia and hypocalcaemia are statistically prominent in association with omeprazole.

The Committee noted that Lareb, the Netherlands Pharmacovigilance Centre has recently published two case reports of hypomagnesaemia/hypocalcaemia in association with omeprazole and reviewed the literature. The Committee was advised that following this review, Medsafe had contacted product sponsors and initiated changes to data sheets. The Committee recommended that a *Prescriber Update* article be published advising prescribers of the recent data sheet changes for omeprazole.

The causal association with omeprazole was considered to be 'probable' for hypomagnesaemia, hypocalaemia.

Recommendation

The Committee recommended that a *Prescriber Update* article be published advising prescribers of the recent data sheet changes for omeprazole.

4.1.1.8 Leflunomide and anosmia, taste loss, rash maculopapular, diarrhoea, coughing (87300)

Discussion

NZPhvC advised that the CARM database includes reports of diarrhoea, skin eruptions, and coughing in association with leflunomide, but none of anosmia or taste loss.

The WHO database includes some reports of loss of smell or loss/alteration of taste, with leflunomide usually the sole suspect medicine.

The product data sheet does not include taste loss or loss/alteration of sense of smell. Taste perversion was noted as occurring in some patients during clinical trials. One published case report of anosmia was found following a literature search. There was no English translation.

The Committee noted that NZPhvC will obtain more information regarding this case.

The causal association with leflunomide was considered to be 'possible' for anosmia, taste loss, diarrhoea, coughing, and 'probable' for rash maculopapular.

4.1.1.9 Acitretin and medication error (87470)

Discussion

NZPhvC advised that the CARM database includes another report of a patient inadvertently being prescribed acitretin, rather than isotretinoin.

The Committee noted that both events occurred after December 2008 when PHARMAC announced changes to prescribing restrictions for acitretin and isotretinoin. They suggested it was possible that acitretinin is probably less familiar to general practitioners that isotretinoin, and that the medicine names had been confused. The Committee had significant concerns about this report and recommended that an article be published in *Prescriber Update* on the indications and use of acitretin.

The causal association with acitretin was considered to be 'certain' for medication error.

Recommendation

The Committee recommended that an article be published in *Prescriber Update* on the indications and use of acitretin.

4.1.2 Fatalities Listing

Members were given a brief description of these reports, with the option of requesting that any particular report/s can be discussed at the current, or a subsequent meeting, if they considered

that there was a safety issue that prescribers should be informed about or regulatory action was required.

The Committee noted the following case reports:

4.1.2.1 Bortezomib (85079)

4.1.2.2 Capecitabine (86711)

4.1.2.3 Clozapine (87481)

4.1.2.4 Oxycodone (87739)

4.1.2.5 Prednisone, leflunomide, azathioprine, methotrexate (86907)

4.1.2.6 Prothrombinex-VF (87648)

4.1.2.7 Risperidone (87737)

4.1.2.8 Risperidone, diazepam (87789)

The Committee discussed report 87789 [..]. The Committee noted that the recommended maximum dose to be given by fortnightly injection was 50mg, and this patient was receiving 75mg. CARM advised that they had received other reports of antipsychotics being used at above recommended doses and also of two antipsychotic medicines being given concurrently. The Committee suggested that it may be timely to consider publishing some information in *Prescriber Update.*

4.1.3 Dianeal death reports

These reports originate from the Marketing Authorisation Holder (MAH) and identify the death of the patient when the reporting nurse informed the MAH that no further solution was required because the patient had since died in the context of end-stage renal failure. The reason for reporting to the MAH was not due to concern that the death may be related to exposure to the solution, but for supply management purposes. Discussion with the MAH established that these cases were recorded and passed on as under ICH regulations, it is a requirement for the MAH to report all cases of death identified whether or not the death is related to the medicine.

Reports of a similar nature were considered at previous MARC meetings. These reports, which were received subsequently, are of the same nature, and are reported here as a matter of record following the recommendation of the MARC.

- 4.1.3.1 Dianeal, icodextrin (86926)
- 4.1.3.2 Dianeal (86927)
- 4.1.3.3 Dianeal, icodextrin (86928)
- 4.1.3.4 Dianeal, icodextrin (86930)
- 4.1.3.5 Dianeal (86930)
- 4.1.3.6 Dianeal (86945)
- 4.1.3.7 Dianeal (87869)
- 4.1.3.8 Dianeal (87870)
- 4.1.3.9 Dianeal (87871)

- 4.1.3.10 Dianeal (87872)
- 4.1.3.11 Dianeal (87873)
- 4.1.3.12 Dianeal, icodextrin (87874)
- 4.1.3.13 Dianeal (87875)
- 4.1.3.14 Dianeal (87876)
- 4.1.3.15 Dianeal, icodextrin (87877)

4.1.4 List reports

These reports are typically due to disease progression, or contain insufficient data for an assessment to be made. They also include non-serious or well known reactions to medicines on the Adverse Reactions of Current Concern (ARCC) list. Members were asked to note these reports, with the option of requesting that any particular report/s be discussed at the current, or a subsequent meeting.

The Committee noted the following case reports:

- 4.1.4.1 Alendronate, phenytoin (86680)
- 4.1.4.2 Alendronate (86843)
- 4.1.4.3 Azathioprine, pentazocine, infliximab (87177)
- 4.1.4.4 Adalimumab (86647)
- 4.1.4.5 Adalimumab (86648)
- 4.1.4.6 Leflunomide (87159)
- 4.1.4.7 Methotrexate, leflunomide (87391)
- 4.1.4.8 Pioglitazone (87285)
- 4.1.4.9 Promethazine (86704)
- 4.1.4.10 Sibutramine (87187)
- 4.1.4.11 Sugammadex (87342)
- 4.1.4.12 Drosperinone/ethinyloestradiol {Yasmin} (87454)

The MARC discussed report 86680, [..] They noted that the product data sheet includes specific information on how the tablets should be taken in order to avoid oesophageal adverse reactions, and prescribers are advised to be sure that the patient has understood the instructions on how to take alendronate.

The Committee noted report 86704 involving promethazine injection. They noted that there had been recent concern internationally about the use of intravenous promethazine and serious tissue injury. A *Prescriber Update* article advising of this was published in November 2009, and the data sheet has been updated. Following the data sheet update, the product sponsor sent out a Dear Healthcare Professional letter to advise of this new safety issue. The Committee considered that this information should be distributed to paramedics and Medsafe agreed to follow this up.

4.2 Quarterly Reports from CARM as at 31 December 2009

Discussion

The Committee noted the quarterly reports from CARM as at 31 December 2009.

NZPhvC advised that they had received a further three reports of withdrawal syndrome in association with venlafaxine, bringing the annual total to six. They also advised that they had received four reports of anxiety in association with bupropion, possibly indicating the re-emergence of this medicine.

4.3 Human Papillomavirus Vaccine (HPV) reports

Discussion

The Committee noted the CARM report of reactions to the HPV vaccine for the period 1 May 2007 to 31 December 2009.

The Committee noted that reports were similar to the pattern of adverse reaction reports received previously.

5. NEW ZEALAND PHARMACOVIGILANCE-RELATED ACTIVITIES - FOR INFORMATION

DHBNZ Safe and Quality Use of Medicines Group. 2010. Newsletter. Volume 6, Number 1

6. INTERNATIONAL PHARMACOVIGILANCE-RELATED ACTIVITIES - FOR INFORMATION

6.1 Australia

- Adverse Drug Reactions Advisory Committee (ADRAC). 2009. Australian Adverse Drug Reactions Bulletin. Volume 28,Number 6
- Advisory Committee on the Safety of Medicines (ACSOM). 2010. Medicines Safety Update. Issue 1

6.2 Canada

- Canadian Adverse Reaction Newsletter. 2010. Volume 20, Issue 1

6.3 Singapore

- Health Sciences Authority (HSA). 2009. Adverse Drug Reaction. Volume 11, Number 3

6.4 United Kingdom

- Medicines and Healthcare products Regulatory Agency (MHRA). 2009. Drug Safety Update. Volume 3, Issue 5
- Medicines and Healthcare products Regulatory Agency (MHRA). 2010. Drug Safety Update. Volume 3, Issue 6
- Medicines and Healthcare products Regulatory Agency (MHRA). 2010. Drug Safety Update. Volume 3, Issue 7

7. OTHER BUSINESS

7.1 Continuing Medical Education

Dr Chris Cameron gave a presentation on statins and dose-response data.

The Acting Chair thanked members and the secretariat for their attendance and closed the meeting at 3.20pm.

Associate Professor M. Rademaker
Acting Chair
Medicines Adverse Reactions Committee

EXHIBIT C

MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
A BUSINESS UNIT OF THE MINISTRY OF HEALTH
www.medsafe.govt.nz

24 May, 2010

Regulatory Affairs Manager
Pfizer
PO Box 57
West Ryde, New South Wales
Australia

Zoloft	TT50-4753 & a, b
Tatig	TT50-8103 & a
Edronax	TT50-6070 & a

Dear Regulatory Affairs Manager,

Re: Review of antidepressant use in pregnancy

I am writing to inform you of the results of a recent review conducted by Medsafe, in conjunction with the Medicines Adverse Reactions Committee (MARC), regarding the use of antidepressant medicines in pregnancy.

This review was prompted by a) the publication of number of studies examining the use of antidepressants in pregnancy and b) the published recommendations of other regulatory authorities.

At the 141st meeting the MARC were presented data investigating the association between congenital anomalies and serotonin reuptake inhibitor use in pregnancy. The MARC concluded that the evidence continued to indicate an association with paroxetine use and congenital anomalies. In addition the MARC considered that there was evidence of an association between fluoxetine use in pregnancy and congenital anomalies. The MARC recommended that the relevant data sheets should be updated. The MARC also recommended that a general warning regarding the risk of congenital anomalies be included in the pregnancy section data sheets for all serotonin reuptake inhibitors.
(http://www.medsafe.govt.nz/profs/adverse/Minutes141.htm#3.1)

Medsafe's review also highlighted that there was also an association between use of these medicines in pregnancy and a number of other adverse outcomes. Therefore you are also requested to ensure that the pregnancy warning section starts with a risk benefit statement and includes information on the following risks:

- Neonatal behavioural syndrome.
- Persistent Pulmonary Hypertension.
- Pre-term birth.

Further review of the use of tricyclic antidepressants in pregnancy revealed similar risks to the use of serotonin reuptake inhibitors[1]. Therefore Medsafe considers that the pregnancy section

[1] Reis M and Kallen B 2010'Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data' Psychological Med doi:10.1017/S0033291709992194.

of data sheets for tricyclic antidepressants, and related antidepressants, should be updated to include warnings regarding the risk of:

- Neonatal behavioural syndrome.
- Congenital anomalies.
- Pre-term birth.

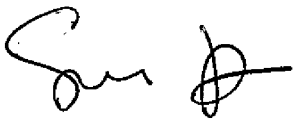
Suggested changes for your data sheets are annexed to this letter.

Please forward a copy of the proposed updated data sheet, with the changes clearly tracked, to me at the address below by **12 July 2010**. Following approval of the changes, a Changed Medicine Notification will need to be submitted to Medsafe.

If this product is not currently marketed in New Zealand, please supply an undertaking in writing that the requested changes will be included in the data sheet prior to any re-launch onto the New Zealand market. Please forward the written undertaking to myself at the address below by **12 July 2010.**

Please confirm receipt of this letter by e-mail. If you have any queries or comments, or if the timing of this request causes any difficulties, please do not hesitate to contact me.

Yours sincerely



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Annex: Requested data sheet changes (strike through indicates removals, additions underlined).

Zoloft (Tatig)

There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, sertraline should be used during pregnancy only if the perceived benefits outweigh the risks, taking into account the risks of untreated depression. Women of childbearing potential should employ an adequate method of contraception if taking sertraline.

If sertraline is used during pregnancy and/or lactation, the physician should be aware of post-marketing reports of symptoms, including those compatible with withdrawal reactions, in some neonates whose mothers had been on SSRI antidepressants, including sertraline.

Neonates exposed to sertraline, other SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalisation, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome.

In a retrospective case-control study the risk for developing persistent pulmonary hypertension in the newborn (PPHN) was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed. There is currently no corroborative evidence regarding the risk of PPHN following exposure to SSRIs in pregnancy. No causal relationship to sertraline has been established.

Epidemiological studies have suggested an increased risk of congenital abnormalities associated with use of SSRIs and SNRIs in pregnancy. The relevance for sertraline treatment remains unknown.

Epidemiological data suggests that the use of SSRIs and SNRIs in pregnancy may be associated with a small but statistically significant increase in pre-term delivery.

Reproduction studies have been performed in rats and rabbits at doses up to approximately 20 and 10 times the maximum daily human mg/kg dose respectively. There was no evidence of teratogenicity at any dose level. At the dose level corresponding to approximately 2.5 to 10 times the maximum daily human mg/kg dose, however, sertraline was associated with delayed ossification processes in foetuses, probably secondary to effects on the dams.

There was decreased neonatal survival following maternal administration of sertraline at doses of approximately 5 times the maximum human mg/kg dose. Similar effects on neonatal survival have been described for other antidepressant drugs. The clinical significance of these effects is unknown.

Reboxetine

Category B1
Reboxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus, taking into account the risks of untreated depression.

Some neonates exposed to SNRIs (Serotonin and Noradrenaline Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalisation, respiratory support, or tube feeding. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. The relevance for reboxetine treatment remains unknown.

Epidemiological studies have suggested an increased risk of congenital abnormalities associated with use of SSRIs and SNRIs in pregnancy. The relevance for reboxetine treatment remains unknown.

Epidemiological data suggests that the use of SSRIs and SNRIs in pregnancy may be associated with a small but statistically significant increase in pre-term delivery.

Recent data suggests the use of SSRIs, after the first 20 weeks of pregnancy may be associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). The relevance for reboxetine treatment remains unknown.

Development studies in rat and rabbits have not shown clear evidence of teratogenic effect at oral dose levels up to 320 and 100 mg/kg/day, respectively. However, in both species, there were increases in post-implantation loss, decreases in mean foetal weight and an increased incidence of skeletal anomalies, including delayed ossification. Compared with human exposure (plasma AUC at the maximum recommended dose), estimated exposure in rats was less than human exposure, and exposure in rabbits was approximately 6 fold (reboxetine, SS enantiomer) and 16 fold (RR enantiomer) higher at the highest dose tested. At the no-effect dose in rabbits (25 mg/kg/day), reboxetine exposure was similar to human exposure. Reboxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.